

New-onset atrial fibrillation in bacteremia is not associated with C-reactive protein, but is predictive of increased mortality

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Abstract

Background: Several studies have associated elevated C-reactive protein (CRP) levels to the occurrence of atrial fibrillation (AF). We sought to estimate the frequency and prognostic impact of AF in patients with bacteremia, and to study the possible association between AF and C-reactive protein (CRP) in this population.

Materials and Methods: We retrospectively evaluated patient-charts of patients with bacteremia with *E.coli* or *S.pneumoniae* admitted to Aker University Hospital in Oslo throughout the period 1994 to 2004. Variables on known cardiac risk factors for AF, signs of AF, mode of conversion of AF, and, if applicable, date of death, were registered. Initial CRP values were categorized into 4 strata. Odds ratios (ORs) of the 3 highest CRP-categories compared with the lowest ones were obtained from logistic models adjusting for known cardiac risk factors for AF. Cox regression analysis was used to compare new-onset AF and death during the first two weeks after hospitalization.

Results: 677 patient charts were studied. 104 patients (15.4%) had new-onset AF. Peak incidence of new-onset AF occurred on the day of admission. Peak CRP values were reached during the two next days. High CRP level at admission did not predict the occurrence of AF. The observed mortality was higher among patients with new-onset AF ($p=0.04$) during the first two weeks after hospitalization.

Conclusions: The frequency of new-onset AF in bacteremia is substantial. Initial CRP levels do not predict new-onset AF. In patients with bacteremia, new-onset AF is associated with increased mortality.

Keywords: C-reactive protein / atrial fibrillation / bacteremia /
inflammation / arrhythmia / human

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting predominantly elderly patients. Its prevalence in a population above 65 years is approximately 5%, representing an increase of prevalence over the last decades which is not expected to come to a halt in the near future.¹ Despite the identification of cardiac risk factors for developing AF such as valvular heart disease, congestive heart failure or hypertensive heart disease¹, not all pathophysiologic mechanisms have yet been fully elucidated. A correlation of an inflammatory state with the occurrence of AF was proposed in 1997², and recently a growing number of studies has shown an association between elevated C-reactive protein (CRP) levels and paroxysmal as well as permanent AF.³⁻⁶ In fact, CRP is not only associated with the existence of AF but it may also predict future development of AF.⁷

In this context the question remains whether CRP also could be a useful marker for the development of AF in systemic infection, which undoubtedly represents an acute inflammatory reaction. We therefore retrospectively evaluated patients with bacteremia representative of a definite invasive infection, *E.coli* and *S.pneumoniae*, thus eliminating or at least reducing false-positive blood cultures due to, e.g., skin flora contamination. After adjusting for known cardiac risk factors for AF, we sought to determine if CRP might be a predictor of new-onset AF in patients with bacteremia. We also compared the mortality in the groups with and without new-onset AF during the first two weeks after hospitalization.

Methods

Objectives and study design

The objectives of this study were to examine the frequency of AF in a patient cohort with a definite invasive infection, and to determine whether CRP may be an independent risk factor for developing AF. Further, we sought to clarify whether new-onset AF has a prognostic impact in patients with bacteremia. We also wanted to determine whether corticosteroid therapy reduce the risk of developing new-onset AF in bacteremia.

By comprehensively registering all well-documented cardiac risk factors in this population, we attempted to correct for those in our regression analysis. The study was designed as a retrospective study of all patient-charts of patients admitted to Aker University Hospital in Oslo, Norway, throughout the period 1994 to 2004, with bacteremia caused by either *E.coli* or *S.pneumoniae*. The Regional Ethics Committee, as well as the Population Data Registry Authority of Norway approved the study.

Study population

The inclusion criteria in our study were as follows: Positive hemoculture of *E.coli* or *S.pneumoniae*, in blood drawn on the day of admission or the day after, and a measured CRP at admission. Patients with bacteremia with *E.coli* or *S.pneumoniae* were selected from the database of our bacteriology laboratory. This database had existed since 1994. Our patient material was restricted to patients who had documented bacteremia on the day of admission or the day after, and who had at least one CRP measurement on the day of admission. The patient-charts were retrieved from the hospital's central archive.

Clinical variables

Anamnestic information. Information on established risk factors for AF was registered. Particularly the following pre-existing conditions were examined: permanent AF, paroxysmal AF, myocardial infarction, angina pectoris, congestive heart failure, arterial hypertension, cardiomyopathy, stroke, and pulmonary embolism. Symptoms of new-onset AF, such as palpitations and dyspnea, were registered. We also registered if the patient were on warfarin treatment, or had been taking corticosteroids in a dose of 10mg or more per day on a regular basis prior to admission.

Documentation of AF and mode of conversion to sinus rhythm. AF was stated if found on a 12-lead ECG. The date of start of new-onset AF was noted. The mode of conversion to sinus rhythm (SR) was registered, as well as the date of conversion.

Chest X-ray and echocardiography. Pulmonary venous congestion was stated if noted in the description of the last chest X-ray taken before the index hospitalization. If an echocardiography was performed within a reasonable time before the hospital stay, we registered left ventricular hypertrophy (LVH) and/or a measurement of the left ventricular ejection fraction (LVEF).

Definitions of AF used. The AF definition followed the newly published AHA-ACC-ESC guideline.⁸ Paroxysmal AF was defined as self-terminating, persistent AF was defined as requiring electrical or pharmacologic intervention to restore sinus rhythm, and permanent AF as the inability for this kind of intervention to restore sinus rhythm. Patients admitted with a history of previously known paroxysmal AF were also registered as having new-onset AF if AF was documented during the index-hospitalization, while patients with a previously known permanent AF were excluded.

CRP-measurements

The CRP values of the individual patients were retrieved from the databases of the Clinical Chemistry Laboratory. These CRP-measurements had been performed by immunoturbidometric assay for automated clinical chemistry analyzers (Roche Diagnostics, Mannheim, Germany). The CRP-levels on the day of admission were categorized into the following strata: 0-50 mg/L, 51-150 mg/L, 151-251 mg/L, and above 250 mg/L. The point in time of later CRP-measurements was expressed in 2 additional categories: CRP2 (i.e., CRP measured on the second or third day of hospital stay), and CRP3 (i.e., CRP measured between day 4 and 7 of the hospital stay).

Analysis of blood culture

Data on positive blood cultures with *S.pneumoniae*, and/or *E.coli* were retrieved from our bacteriology laboratory database. In case of a patient having more than one episode of bacteremia, either the first or the last episode was registered. A small number of patients had episodes of both *E.coli* and *S.pneumoniae* bacteremia. Here the two bacteria types were selected every other time. By this procedure each patient was represented uniquely, by only one episode of bacteremia, and by only one bacterium. The blood culture system used in the period was Bactec 9240 (Becton & Dickinson, Sparks, MD, USA). Further identification of the positive blood cultures followed standard procedures of the laboratory. Growth of possible *S.pneumoniae* was confirmed by typical fenotype and sensitivity to optochin and later also by agglutination test (Slidex pneumo-Kit, BioMérieux, Lyon, France). *E.coli* was identified by a three tube method for identification of Gram-negative rods,⁹ or by api20E (BioMérieux).

Statistics

Chi-square tests were used to compare groups with categorical data. Odds ratios (ORs) for the three highest CRP-categories compared with the lowest with 95% confidence intervals (95% CIs) were obtained from logistic models adjusting for known cardiac risk factors for AF. Tests for trend were obtained from logistic models treating CRP-categories as a continuous variable. Cox regression was used comparing new onset AF and death during the first two weeks after hospitalization. All tests were computed using the SPSS - 14.0 software (SPSS Inc., Chicago, IL, USA). P-values <0.05 were considered significant. Receiver-operating characteristic (ROC) curves were used to evaluate the overall diagnostic performance of measured CRP-levels.

Results

759 patients fulfilled the inclusion criteria. Of these 82 patients were excluded either because of inadequate information in the charts, or due to the fact that the patient-chart was unavailable (i.e., patients were hospitalized concomitantly with our chart study period). This resulted in a total patient cohort of 677 patients.

Baseline characteristics

Baseline characteristics of the cohort are outlined in Table 1. The age of the patients ranged from 20 to 100 years (mean 69.1 years). 57% of the patients were women and 43% were men. *E.coli* bacteremia was documented in 66.5% of the patients and *S.pneumoniae* in 33.5%.

New-onset AF

New-onset AF occurred in 104 patients (15,4%), of which 61 were women (9.0 %) and 43 men (6.4 %). Age in the new-onset AF group ranged from 30 to 93 years (mean 77.0 years). 18 (17.3%) of the patients with new-onset AF had a previously diagnosed paroxysmal AF with a new episode of AF at admission. The peak incidence of new-onset AF was on the second to third day of hospital stay.

Of symptoms related to AF, such as dyspnea, palpitations, vertigo or syncope, the new-onset AF group reported the symptoms more often than the whole cohort. The AF episode was documented by 12-lead EKG in 86.5% of the cases, in the rest by a physician's clinical diagnosis. The heart rate in these patients varied from 43 to 190 with a mean of 122.

Spontaneous conversion from AF to sinus rhythm occurred in 35 patients (33.7% of all AF patients), while 40 patients (38.5%) were treated pharmacologically before conversion to sinus rhythm, and 1 patient (1%) needed electrical (DC) conversion. The remainder (28 patients, 26.9%) persisted in AF.

Established risk factors for AF

The frequencies of previously established cardiac risk factors for AF are listed in Table 2. In both the new-onset AF group and in the group without new-onset AF, more than a half of the patients had cardiovascular disease at admission, either anamnestically or as documented by chest X-ray or echocardiography. In the entire patient cohort 47.7% had at least one of these conditions, while the corresponding number was 66.4% in the new-onset AF group.

CRP as a possible risk factor for AF

The CRP values on the day of admission ranged from 2 mg/L to 629 mg/L, with a median of 206.0 mg/L. In the new-onset AF subgroup the values ranged from 2 mg/L to 629 mg/L, with a median of 211.5 mg/L. The CRP-value distribution is shown in Figure 1. The majority of new-onset AF occurred on the day of admission. (Figure 2) Peak CRP values were reached during the two next days.

The ROC curve of the diagnostic performance of the initial CRP-levels is depicted in Figure 3. The areas under the curves were 0.55 and 0.53 for CRP levels treated as continuous and categorical variables, respectively.

The observed odds ratios for new-onset AF in the three highest CRP-categories relative to the lowest were 1.34 (95% CI: 0.68-2.67), 1.28 (95% CI: 0.65-2.52) and 1.47 (95% CI: 0.87-3.17), respectively. There was no significant trend in this figures ($p = 0.24$). Adjusting for earlier known cardiac risk factors did not have any impact on the estimates.

Concomitant corticosteroid treatment

In the total patient group 34 patients had been taking oral corticosteroids (methylprednisolone > 10 mg) on a daily basis prior to the actual admission. Four of these patients had new-onset AF. There was no significant difference between the new-onset AF group and the one without new onset AF.

New-onset AF and survival

46 persons died during the first four days after hospitalization. This number increased to 78 after two weeks. The percentage of patients still alive during the first two weeks after hospitalization is shown in Figure 4. The hazard ratio was 2.24 (95% CI: 1.37-3.66, $p=0.001$) among patients with new-onset AF relative to patients without new-onset AF. When adjusting for sex and age above 65 years the hazard ratio was 1.70 (95% CI: 1.03-2.79, $p=0.04$).

Discussion

While atrial fibrillation (AF) in clinical practice frequently is viewed as an indirect sign of infection, particularly in the elderly patients, this experience is not scientifically well documented. Postoperative AF, on the other hand, was reported as early as in the 1970's.¹⁰ In one report analyzing patients after off-pump coronary artery bypass grafting (CABG), the frequency of postoperative AF in conjunction with an infection was 71.4%, in contrast to 21.4% if no infection was demonstrated microbiologically.¹¹ In another study of 460 unselected patients admitted to a surgical intensive care unit (ICU), significantly more patients with postoperative AF experienced sepsis and septic shock than the patients without postoperative AF.¹² And in a large multi-center study of patients that underwent CABG, the only factor associated with infection was recurrent postoperative AF.¹³

Our study, to our knowledge, is the first to report on the frequency of new-onset AF in a large population of patients with severe bacterial infection as apparently primary event. The finding of a 15.4% frequency of new-onset AF in this population is quite substantial, approximately equaling the reported incidence of postoperative AF after off-pump CABG (17.6%), after resection of colorectal cancer (13.7%) or cancer of the lung (19.8%).¹⁴⁻¹⁶ It is somewhat lower than the incidence after conventional CABG (appr.30-40%) and after resection of cancer of the esophagus (22%).^{16;17} And it is definitely higher than the occurrence after total hip or knee arthroplasty (3.1%).¹⁸

The at least partial involvement of inflammation in the pathogenesis of AF seems to be widely acknowledged based on clinical, epidemiological, pharmacological and histological observations.¹⁹ These observations are related to both paroxysmal and

permanent AF, as well as new-onset AF after coronary surgery. Intriguingly, many of these studies are based on associations between AF and CRP.

Our cohort of 677 patients with bacteremia with *E.coli* or *S.pneumoniae* is a population of indisputable high-grade inflammation. It may therefore appear astounding that no association between early CRP and increased risk of new-onset AF seems to materialize in our data. Neither did maximum CRP level coincide with peak incidence of new-onset AF. Baseline CRP is shown to be a risk indicator for AF after coronary surgery,²⁰ and lowering of baseline CRP with atorvastatin appears to be effective in eliminating paroxysmal AF in a significant proportion of patients, although other mechanisms may be operative.²¹ It has also been shown that the maximum postoperative CRP level is reached on the same day as the peak incidence of AF.² In the same study, however, the crude CRP levels on day 2 were not associated to AF. And despite the fact that interleukin-6 polymorphisms apparently affect the development of postoperative AF, early postoperative CRP does not.²² In yet another investigation scrutinizing AF after CABG there were no differences in the degree of the inflammatory response, included CRP, between patients who did and those who did not develop AF.²³

It is unknown to what extent the mechanisms for developing AF are the same in paroxysmal, permanent and new-onset AF. The discrepant results as regards CRP being a risk factor for AF in chronic, subclinical inflammation *versus* in acute inflammation, may point to different pathophysiologic mechanisms. Thus, statements on the association of inflammation, CRP and AF should be treated with caution. We do not doubt that inflammation be involved, but there is little evidence that CRP *per*

se has a pathophysiologic function in new-onset AF during acute inflammation. Rather, it seems that inflammatory mediators upstream of CRP may be involved through so-called innate immunity reactions. This notion is in agreement with the results of the aforementioned IL-6 polymorphism study, and the finding of a link between postoperative complement activation and postoperative AF.^{2;22} Further, experimental support of this view stems from the finding that arachidonic acid reduces conduction velocity in atrial tissue.²⁴ In this context it is interesting to note one recent investigation showing that in the absence of elevated complement components, no statistical association was found between high CRP levels and permanent AF, challenging even the idea that CRP is closely associated to the development of permanent AF.²⁵

Corticosteroid therapy has been associated with reduced risk of recurrent and permanent AF, conceivably due to reduction of CRP.²⁶ In an animal model of experimental sterile pericarditis methylprednisolone significantly reduced the incidence of AF.²⁴ As corticosteroids have a broad anti-inflammatory action, we expected to find a lower incidence of new-onset AF in patients that had been treated with corticosteroids. However, we did not find such an association. On the other hand, the massive inflammatory chain of events during bacteremia may have overruled the anti-inflammatory action of a normal daily dose of methylprednisolone. Corticosteroid treatment is an unresolved issue in sepsis²⁷, and indeed it has not been evaluated yet whether patients who are receive high doses of corticosteroids do have a lower incidence of new-onset AF than the ones without this treatment.

Chronic AF is associated with increased mortality, even after adjustment for preexisting cardiovascular conditions,²⁸ as is postoperative AF.^{12;17;29;30} The level of increased mortality in these studies compares favorably to our finding of an almost doubled mortality risk in patients with new-onset AF as compared to those without new-onset AF. In the before mentioned study of new-onset AF following surgical esophagectomy, AF was not the cause of death, leading the authors to conclude that atrial arrhythmias are simply markers of increased mortality and morbidity.¹⁷ This is consistent with findings in trauma patients admitted to an ICU, in whom AF is associated with the systemic inflammatory response syndrome (SIRS), sepsis, acute renal failure and higher scores of disease severity. The authors of this study suggest that the onset of AF should be considered a surrogate marker of grave complications, rather than conferring a major effect on mortality in itself.²⁹

Taken together, the here presented results do not identify CRP as a predictor of new-onset AF in patients suffering from bacteremia. On the other hand, the occurrence of AF during bacteremia should be viewed as a prognostic marker of adverse outcome. The issue of a possible association of inflammation, CRP and AF certainly deserves further scrutiny.

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Tables and Figures

Table 1

Baseline characteristics

	Entire cohort	Patients without new-onset AF	Patients with new-onset AF
	(n=677)	(n=571)	(n=104)
Sex			
male	291 (43.0%)	248 (43.3%)	43 (41.3%)
female	385 (56.9%)	324 (56.5%)	61 (58.7%)
Age			
Age 20-64	229 (33.8%)	218 (38.0%)	11 (10.6%)
Age 65-79	196 (29.0%)	154 (26.9%)	42 (40.4%)
Age >80	252 (37.2%)	201 (35.1%)	51 (49.0%)
Bacteria			
<i>E.coli</i>	450 (66.5%)	384 (67%)	66 (63.5%)
<i>S.pneumoniae</i>	227 (33.5%)	189 (33%)	38 (36.5%)
Symptoms			
Dyspnoe	135 (19.9%)	99 (17.3%)	36 (34.6%)
Palpitations	4 (0.6%)	0 (0.0%)	4 (3.8%)
Vertigo	39 (5.8%)	8 (4.9%)	11 (10.6%)
Syncope	13 (1.9%)	9 (1.6%)	4 (3.8%)

Table 2**Established risk factors for AF**

	Entire cohort	Patients without new-onset AF	Patients with new-onset AF	p-value*
Permanent AF	38 (5.6%)	38 (6.6%)	0 (0.0%)	
Paroxysmal AF	40 (5.9%)	19 (3.3%)	21 (20.2%)	<0.0005
Myocardial infarction	90 (13.3%)	73 (12.7%)	17 (16.3%)	0.319
Angina pectoris	93 (13.7%)	70 (12.2%)	23 (22.1%)	0.007
Congestive heart failure	79 (11.7%)	62 (10.8%)	17 (16.3%)	0.106
Hypertension	152 (22.5%)	114 (19.9%)	38 (36.5%)	<0.0005
Cardiomyopathy	20 (3.0%)	12 (2.1%)	8 (7.7%)	0.002
Hyperthyreosis	2 (0.3%)	2 (0.3%)	0 (0.0%)	0.546
Cerebrovascular disease	94 (13.9%)	77 (13.4%)	17 (16.3%)	0.430
COPD	72 (10.6%)	57 (9.9%)	15 (14.4%)	0.173
Pulmonary embolism	10 (1.5%)	10 (1.7%)	0 (0.0%)	0.175
Alcohol	46 (6.8%)	40 (7.0%)	6 (5.7%)	0.406
Age > 65 years	443 (65.4%)	350 (61.1%)	93 (89.4%)	<0.0005
X-ray subgroup	n=591	n=491	n=100	
	45 (7.6%)	37 (7.5%)	8 (8.0%)	
Pulmonary venous congestion on x-ray				
Echo subgroup	n=69	n=48	n=21	
LVH on echocardiography	22 (31.9%)	19 (39.6%)	3 (14.3%)	
LVEF<45%	16 (34,0%)	9 (28,1%)	7 (46.7%)	

p-value* comparing patients with and without new-onset AF

Figure legends

Figure 1. Distribution of CRP values on the day of admission

Figure 2. Number of new onset AF and mean CRP at different days of hospital stay.

Figure 3. Comparison of sensitivity and 1 – sensitivity for initial CRP levels measured both on continuous and categorical scale.

Figure 4. Survival during the first two weeks after hospitalization

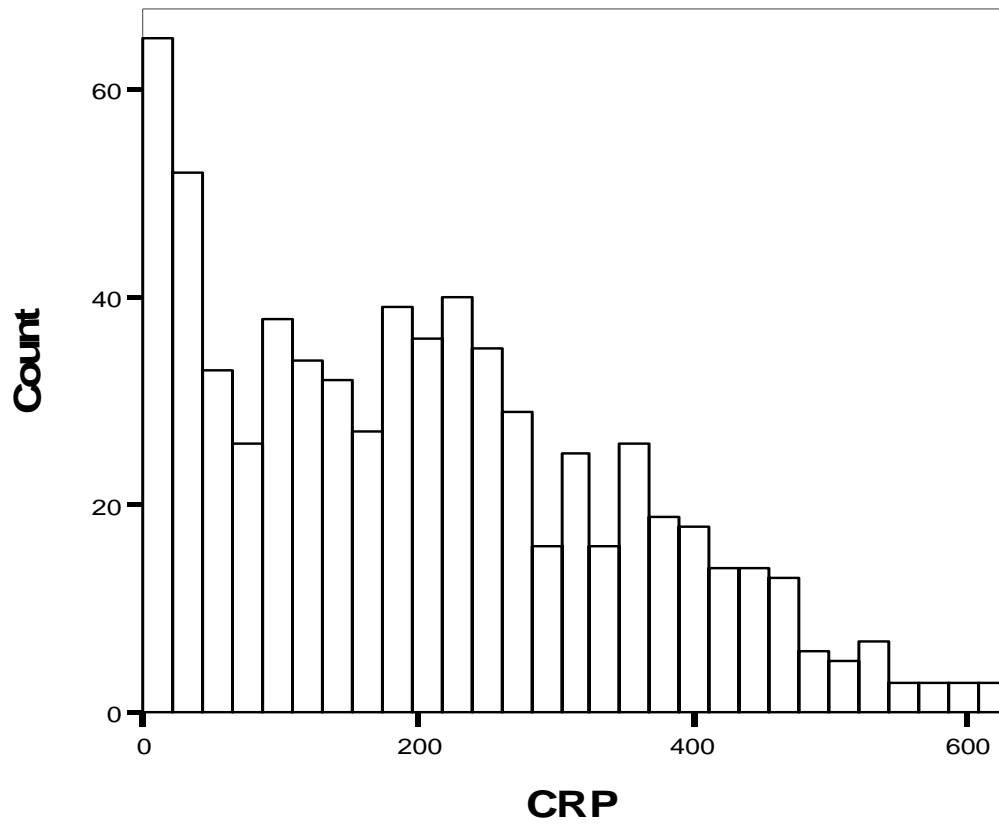
Figure 1

Figure 1. Distribution of CRP values on the day of admission

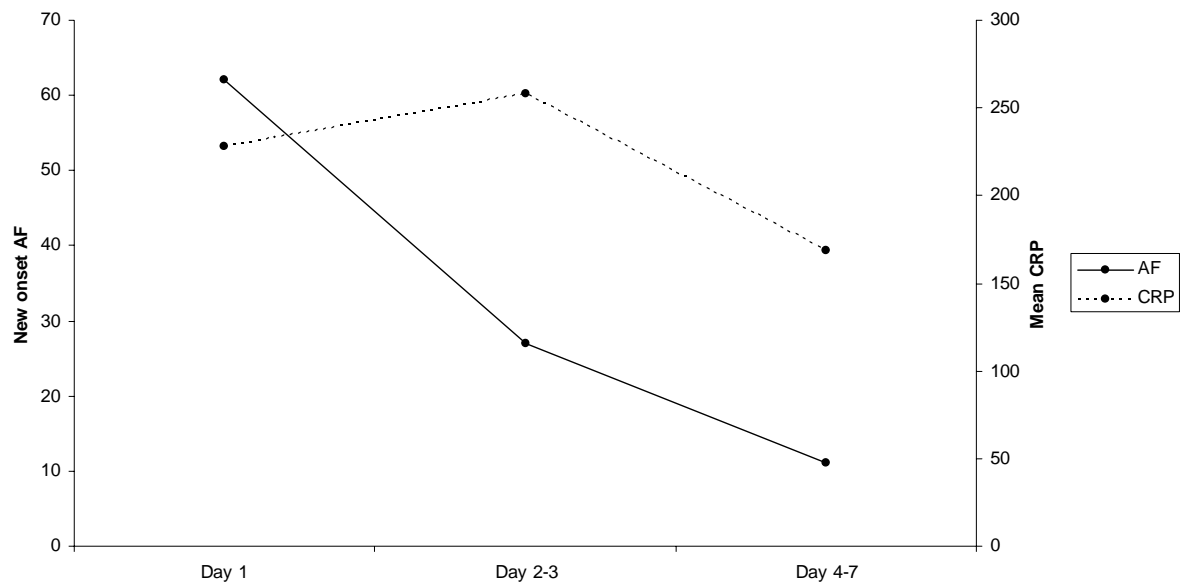
Figure 2

Figure 2. Number of new onset AF and mean CRP at different days of hospital stay.

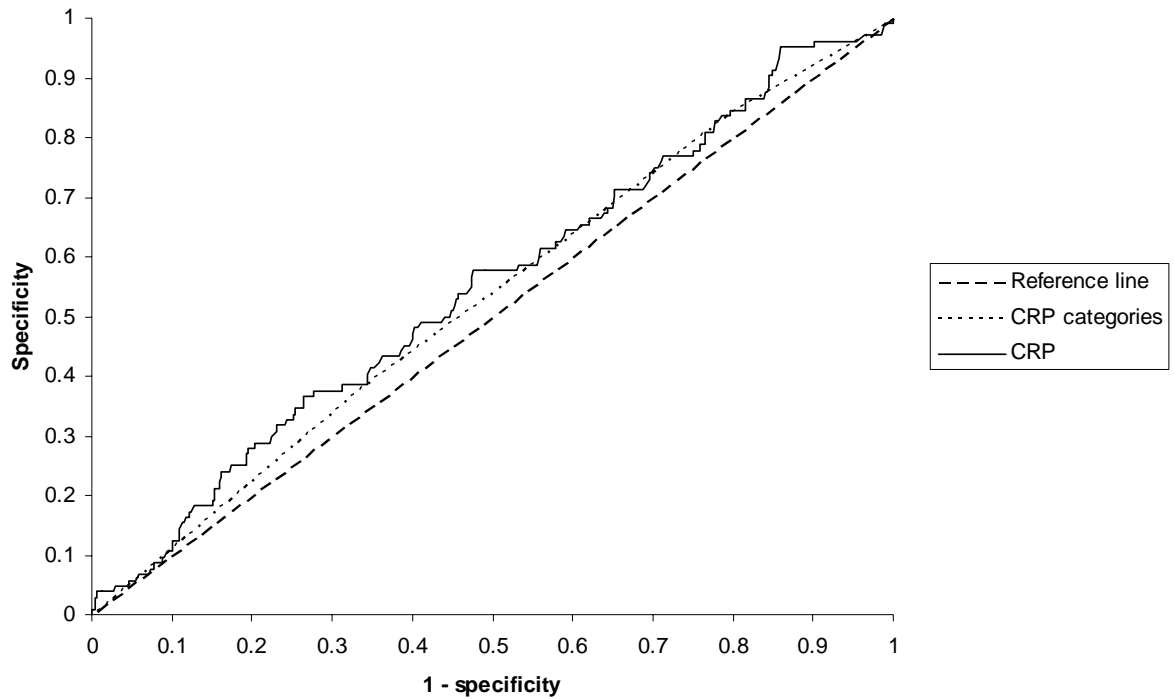
Figure 3

Figure 3. Comparison of sensitivity and 1 – sensitivity for initial CRP levels measured both on continuous and categorical scale.

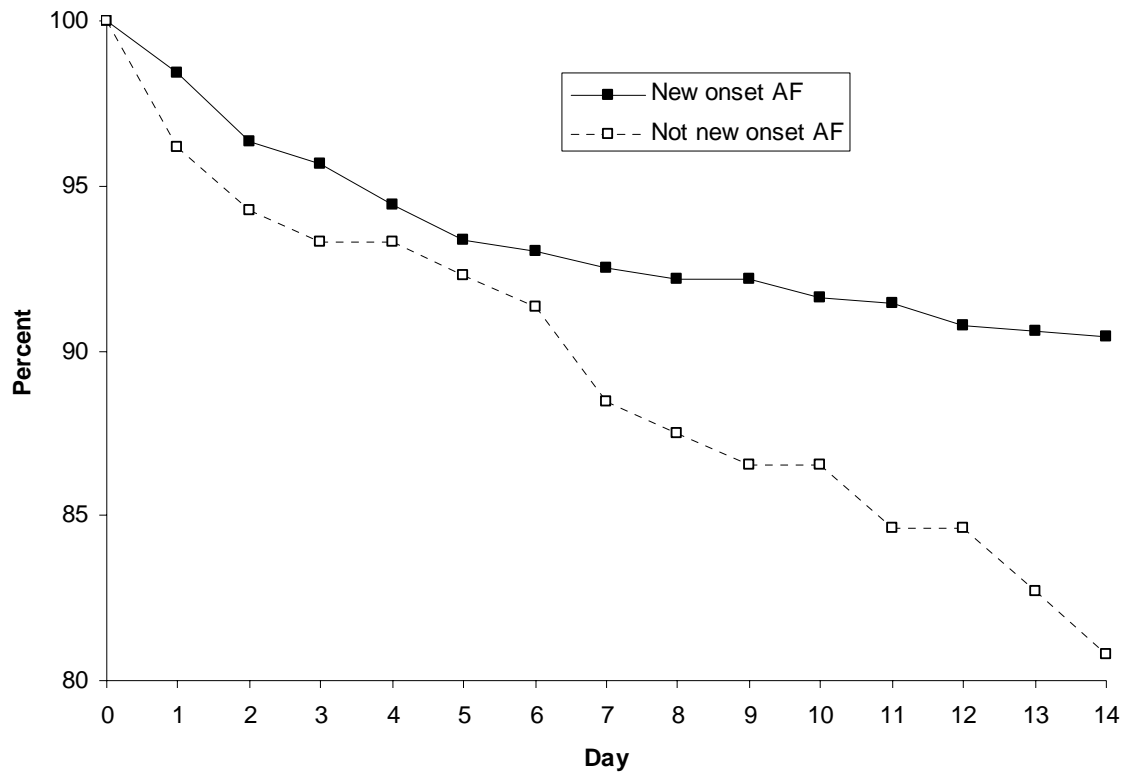
Figure 4

Figure 4. Survival during the first two weeks after hospitalization